Blue Rubber Bleb Nevus Syndrome

Surgical Eradication of Gastrointestinal Bleeding

Steven J. Fishman, MD, FACS,† C. Jason Smithers, MD,*† Judah Folkman, MD, FACS,*† Dennis P. Lund, MD, FACS,‡ Patricia E. Burrows, MD,†§ John B. Mulliken, MD, FACS,*† and Victor L. Fox, MD†‖*

Objective: We report the largest clinical experience to date of surgically treated patients with blue rubber bleb nevus syndrome (BRBNS).

Summary Background Data: BRBNS is a rare congenital disorder presenting with multifocal venous malformations of the skin, soft tissues, and gastrointestinal (GI) tract. Patients with BRBNS develop anemia from chronic GI bleeding, and require lifelong treatment with iron and blood transfusions. An aggressive surgical approach to treat the GI venous malformations of BRBNS has been considered unlikely to be successful because of the large number of lesions, their position throughout the GI tract, and the likelihood of recurrence. Based on our belief that eradicated lesions would not recur, we undertook the removal of all GI tract lesions in an effort to eliminate bleeding.

Methods: Ten patients with BRBNS were treated from 1993 to 2002. Lesions were identified using complete GI endoscopy. The multiple venous malformations were removed by a combination of wedge resection, polypectomy, suture-ligation, segmental bowel resection, and band ligation.

Results: Patient ages ranged from 2 to 36 years, and patients received an average of 53 prior blood transfusions. A mean of 137 focal GI venous malformations per patient were resected at operation (range 4–557), with a mean operative duration of 14 hours (range 7–23 hours). Only 1 patient who had a less extensive procedure developed recurrent GI bleeding. The mean follow-up period was 5.0 years (range 2.9–10.3 years).

Conclusions: We believe that an aggressive excisional approach is indicated for the venous anomalies that cause GI bleeding in BRBNS.

(*Ann Surg* 2005;241: 523–528)

Blue rubber bleb nevus syndrome (BRBNS) is a rare vascular anomaly syndrome consisting of multifocal venous malformations (VM). The malformations are most prominent in the skin, soft tissues, and gastrointestinal (GI) tract, but may occur in any tissue. This association of "hemangiomas" of the skin and GI tract was first reported in 1860,[1] and fully characterized by William Bean in 1958, giving rise to the eponym "Bean syndrome."[2] The cutaneous lesions of BRBNS are generally small, measuring less than 1–2 cm, and blue to purple in color. Bean was the first to draw attention to the unique quality of these compressible cutaneous lesions that he labeled as "blue rubber-bleb nevi." A patient may have from several to hundreds of cutaneous lesions. Nonetheless, the GI lesions of BRBNS are more clinically relevant than the skin and soft tissue lesions. Patients usually exhibit GI bleeding at an early age that continues throughout their life. Massive sudden hemorrhage rarely occurs. Rather, patients are chronically anemic, requiring lifelong iron replacement and repeated blood transfusions. Although there are reported cases that appear to have an autosomal dominant transmission,[3–6] most cases are sporadic.

A variety of therapeutic strategies have been proposed for the management of GI bleeding in BRBNS, including antiangiogenic agents and endoscopic approaches.[7–16] However, no particular method has been demonstrated to be reliably effective in reducing bleeding or in permanently controlling blood loss. Surgical resection has been condemned as overly aggressive and unhelpful because of the belief that lesions would recur after removal.[9,17–21]

Confusing terminology has historically obscured the diagnosis and treatment of vascular anomalies, whereas the biologic classification of these anomalies as either vascular tumors or malformations has greatly advanced this field.[22]

From the *Departments of Surgery, §Radiology, ‖Gastroenterology, and the †Vascular Anomalies Center, Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts; and the ‡Department of Surgery, University of Wisconsin Children's Hospital, WI.

No external funding was required for this study, and there are no financial disclosures.

Reprints: Steven J. Fishman, M.D., 300 Longwood Avenue, Fegan-3, Children's Hospital Boston, Department of Surgery, Boston, MA 02115. E-mail: steven.fishman@childrens.harvard.edu.

ISSN: 0003-4932/05/24103-0523
DOI: 10.1097/01.sla.0000154689.85629.93

Because the vascular lesions of BRBNS are consistent with congenital vascular malformations rather than proliferative tumors, it is not surprising that antiangiogenic agents such as corticosteroids and interferon are not effective. However, congenital malformations, once resected, should not recur. Based on our understanding of the natural history, we deduced that the rational treatment to eliminate bleeding for patients with BRBNS is an aggressive approach encompassing removal of all GI lesions.

MATERIALS AND METHODS

All patients in this report presented to the multidisciplinary Vascular Anomalies Center at Children's Hospital Boston with a history of GI bleeding and a known or suspected vascular anomaly of the GI tract. Each was evaluated and treated by the same team of specialists between 1993 and 2001. The diagnosis of BRBNS was established by clinical history, physical appearance of cutaneous lesions, imaging studies,[23,24] and the pathognomonic endoscopic appearance of the gastrointestinal lesions. (Fig. 1, A and B) In all patients, the diagnosis was eventually confirmed histologically. All patients had chronic anemia requiring the continual administration of iron and/or blood transfusions.

Patients underwent endoscopic evaluation including flexible fiberoptic esophagogastroduodenoscopy, colonoscopy, and intraoperative flexible or rigid enteroscopy. An attempt was made to eradicate every identifiable vascular malformation from the stomach to the anus. A combination of operative and endoscopic resection techniques was used. In some cases, the endoscopic procedures were performed at a separate setting from the laparotomy. However, in most of the later cases, the endoscopic and open laparotomy procedures were performed simultaneously to ensure visualization of all GI tract lesions and proper selection of the safest and most efficacious therapeutic technique. To maintain maximal bowel length, the use of bowel resections was minimized and restricted to areas in which there were extremely high densities of lesions.

All patients were managed and followed by a single surgeon. Quantitative data were tabulated by review of each patient's medical records and operative notes. Each patient was contacted to ensure completeness and accuracy of data. Research protocol and patient contact were approved by the Committee on Clinical Investigation, Children's Hospital Boston.

RESULTS

Patient Characteristics

Ten patients were operated on between 1993 and 2001 (Table 1). In addition to iron replacement and blood transfusions, 4 patients in this series received prior medical therapy aimed at inhibition of GI bleeding. Three patients had received interferon-α; 1 was also treated with danazol. Another patient had received oral contraceptives for this purpose. Three patients in the series had prior laparotomies for complications related to their GI venous malformations. One patient had 3 previous operations for GI bleeding, one of which included an ileal resection of 80 cm. Another patient required a sigmoid colostomy for colonic obstruction after

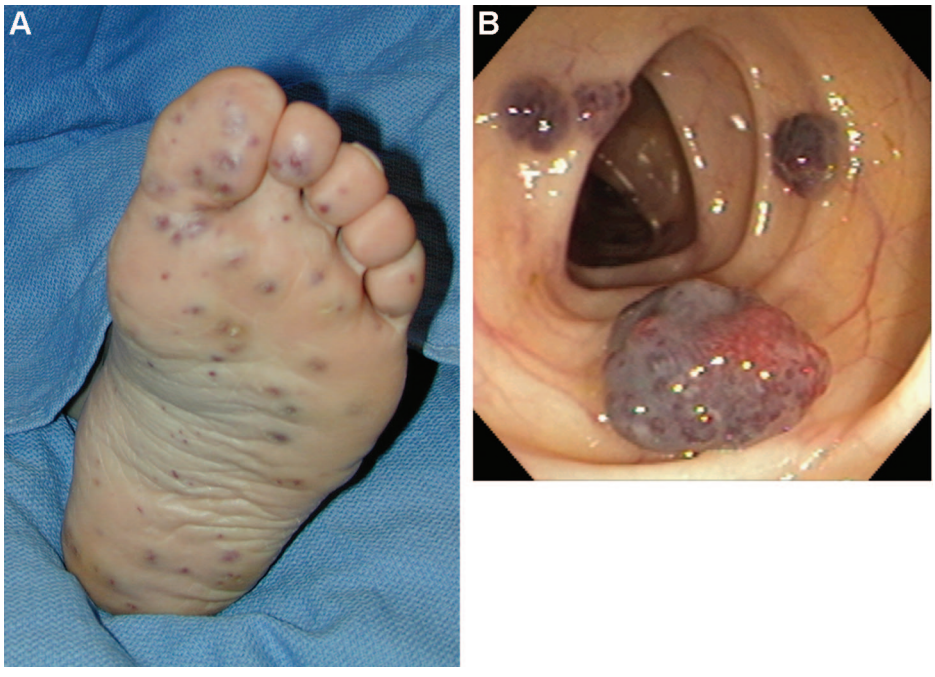

FIGURE 1. (A) Characteristic venous malformations of blue rubber bleb nevus syndrome (BRBNS) in a classic location on the sole of the foot. (B) Endoscopic appearance of intestinal venous malformations from BRBNS.

TABLE 1. Preoperative Characteristics of 10 Patients With Blue Rubber Bleb Nevus Syndrome

Age at time of operation	2–36 yr (mean 16 yr)
Gender	4 male, 6 female
Age at diagnosis of GI bleeding	Birth–19 yrs (mean 5 yrs)
Lowest hemoglobin before operation	2.2–8.8 g/dL (mean 5.2 g/dL)
Prior blood transfusions	1–over 200 units (mean 53, median 28)
Prior endoscopies (per patient)	1–6 (mean 2.9)
Prior endoscopic treatments	5/10 patients
Prior operations for GI lesions	3/10 patients
Prior medical therapy to inhibit GI bleeding	4/10 patients
Prior surgical resection and/or sclerotherapy of VM of skin and soft tissues	8/10 patients

GI, gastrointestinal; VM, venous malformation.

percutaneous sclerotherapy of a VM involving the retroperitoneum. Lastly, one patient had a prior small bowel resection for intussusception caused by a polypoid VM serving as the lead point.

The patients in this series exhibited a wide range of lesions of the skin and soft tissues associated with BRBNS. Affected tissues and organs included skin, subcutaneous tissue, muscle, bone, joint, parotid gland, thymus, lung, liver, gallbladder, pancreas, spleen, mesentery, pelvis, and retroperitoneum. One patient had no venous malformations of the skin whatsoever; others had required a multitude of prior procedures including sclerotherapy and operative resection for VM of the skin and soft tissues.

Operative Intervention

Resection techniques included full-thickness wedge excision, polypectomy via enterotomy, suture ligation via enterotomy, segmental bowel resection, and endoscopic band ligation (Table 2). Some gastric, duodenal, and colonic lesions examined endoscopically were band-ligated if operative evaluation of the viscera confirmed the absence of transmural involvement of the lesions. In other cases, endoscopic visualization was used to localize the lesions, which were marked with serosal sutures or a marking pen. The lesions were then removed through a gastrotomy, duodenotomy, or colotomy. Endoscopic visualization of the small intestine was performed in the early patients with a sterile flexible fiberoptic colonoscope advanced through an enterotomy. In later patients, a 10-mm, 0-degree rigid laparoscope was used for this purpose. Most transmural lesions were removed by wedge resection. Mucosal and submucosal lesions were exposed by sequentially intussuscepting the bowel through enterotomies performed at the site of wedge resection of transmural lesions (Fig. 2, A and B). No enterostomies or colostomies were necessary.

The mean operative duration was 14 hours (range 7–23). A mean of 137 GI venous malformations were resected at operation (range 4–557). The VM were distributed throughout the GI tract in all sections from mouth to anus. The small and large intestines were involved in every patient and represented the 2 sites with the largest numbers of lesions (Table 3). Eight of 10 patients had total GI endoscopy, either intraoperatively or combined preoperatively and intraoperatively. The most recent 6 patients had complete endoscopy during the operative procedure. The first 2 patients in the series did not have small bowel enteroscopy as part of their evaluation or operation; rather, the external appearance and

TABLE 2. Data Regarding Operative Interventions to Treat Gastrointestinal Venous Malformations in 10 Patients With Blue Rubber Bleb Nevus Syndrome

Operative duration	7–23 h (mean 14)
Estimated blood loss	Minimal–400 mL (mean 150 mL)
Total GI endoscopy	8/10 patients (first 2 patients did not have intraoperative enteroscopy)
Endoscopic banding	3/10 patients (range 5–54 lesions/patient)
Enterotomies per patient	4–27 (mean 18)
Lesions treated by operative polypectomy*	9/10 patients (range 1–150 lesions/patient, mean 35 lesions/patient)
Lesions treated by suture ligation*	3/10 patients (range 5–320 lesions/patient, median 7 lesions/patient)
Lesions treated by full-thickness wedge excision	10/10 patients (range 4–26 lesions/patient, mean 17 lesions/patient)
Small bowel resection	2/10 patients (10 cm and 20 cm total)
Colectomy	1/10 patients (patient had left colectomy for 65 lesions)
Other procedures for intraabdominal venous malformations	6/10 patients (4 had hepatic wedge resections, 3 had cholecystectomy, 2 had resection of mesenteric lesions, 1 had transduodenal sphincteroplasty)

*In one patient with 557 lesions, the distribution between polypectomy and suture ligation techniques was estimated.
GI, gastrointestinal.

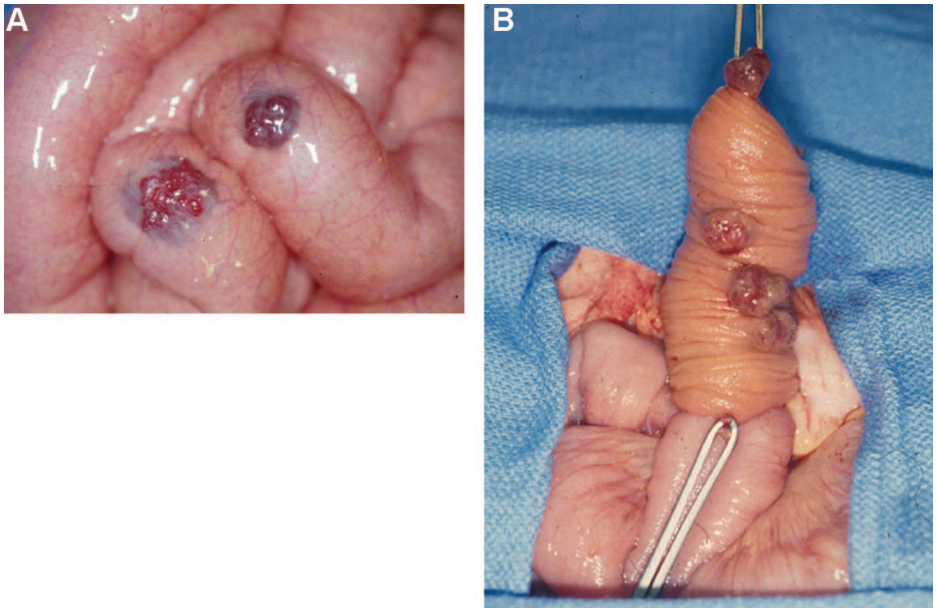

FIGURE 2. (A) Serosal surface of small intestine venous malformations at time of exploratory laparotomy. (B) The technique of intussusception of the bowel to access multiple venous malformations for resection and limit the total number of enterotomies needed for the procedure.

palpation of the small intestine was relied upon to identify lesions. Six patients had resection of intraabdominal VM in locations other than the GI tract. There were 4 hepatic wedge resections, 3 cholecystectomies, and 2 mesenteric resections. One patient had transduodenal sphincteroplasty for a lesion involving the ampulla of Vater.

The perioperative complications included 2 incisional wound infections that were treated by open packing. Five of 10 patients received perioperative blood transfusions of 1 to 2 units each. The mean length of hospital stay was 12 days (range 7–24 days). There was no other short-term or long-term morbidity.

Outcomes

Follow-up evaluation ranged from 2.9 to 10.3 years (mean 5.0 years). No patients were lost to follow-up. The most recent hemoglobin level for each patient ranged from 11.3 to 15.7 (mean 13.0). Patients have unanimously reported renewed energy and vigor after their operations once their hemoglobin levels returned to the normal range. Only 1 patient developed a recurrent blood transfusion requirement, beginning 2 years after his operative procedure. This patient, one of the earliest in the series, did not have small bowel enteroscopy during the operation. Lesions were resected based on external examination and palpation of the bowel. The entirety of the intraluminal surface was thus not visualized, and it is likely that some lesions were unrecognized and therefore unresected. Although he has not yet returned for endoscopic evaluation, it is likely that his recurrent bleeding is due to residual VM in the small intestine.

Two other patients have recurrent or residual disease. One patient's procedure was intentionally staged because of the large number of lesions remaining 21 hours into the operation. This patient had 245 lesions resected during the first-stage procedure and is known to have many remaining small bowel and colonic lesions. The second-stage operation is not yet planned given a stable hemoglobin level, absence of symptoms, and no transfusion requirement since the initial operation more than 3 years ago. The other patient has not experienced clinical bleeding, but underwent upper endoscopy for abdominal discomfort and was incidentally noted to have VM in her stomach and duodenum. She subsequently underwent colonoscopy, which demonstrated lesions in the lower GI tract as well, predominantly in the rectum. Wireless capsule endoscopy also demonstrated scattered lesions throughout the small bowel with a lesser density than seen in the stomach and rectum. Although this patient had undergone complete intraluminal visualization at the time of operation,

TABLE 3. Distribution of Venous Malformations Throughout the Gastrointestinal Tract of 10 Patients With Blue Rubber Bleb Nevus Syndrome

Location	Number of Patients (n = 10)	Number of Lesions per Patient (mean, median)
Esophagus	3	0–3 (0.6, 2)
Stomach	7	0–22 (6.4, 7)
Duodenum	7	0–14 (2.4, 2)
Small bowel	10	3–337 (90, 41)
Colon	10	1–143 (33, 13)
Rectum	5	0–36 (4.4, 3)
Total	10	4–557 (137, 43)

GI, gastrointestinal.

many of her lesions were addressed by band ligation or suture ligation rather than resection to limit operative duration. She had 557 lesions, and complete excision, as had been performed in the prior patients, would have required 2 staged procedures, which the patient strongly desired to avoid.

An additional 22 patients with BRBNS are currently being followed, but have not required intervention because of minimal bleeding without severe anemia. There are no cases of familial BRBNS in this series, other than 1 set of identical twins, both of whom are included in the operative series.

DISCUSSION

Vascular anomalies are, in general, poorly understood by practitioners of most medical specialties. The classification and nomenclature of vascular anomalies have historically been inconsistent and confusing. The term "hemangioma" has traditionally been inappropriately applied widely to a large variety of disparate vascular lesions. Descriptive modifiers, such as "capillary," "cavernous," "strawberry," and "lympho-" are frequently added to the term "hemangioma." However, most lesions so described are not hemangiomas at all. A biologic classification first proposed in 1982 is based on clinical behavior and histologic appearance.[22] Vascular anomalies are broadly divided into 2 major groups–tumors and malformations. The predominant tumor type is the hemangioma of infancy. Hemangiomas follow a predictable characteristic life cycle. These predominantly cutaneous lesions become apparent in the first week or 2 postnatally, proliferate for 10–14 months, then stabilize and involute over the subsequent 3–6 years. These lesions never persist beyond early childhood. Multiple cutaneous hemangiomas are occasionally associated with visceral lesions, most commonly in the liver and less frequently in the bowel. With the exception of hepatic lesions, the need for treatment of hemangiomas of the GI tract is exceedingly rare. Proliferation of hemangiomas can be inhibited and involution hastened using antiangiogenic therapy, such as corticosteroids or interferon-α.

Vascular malformations result from errors of vascular morphogenesis and are named by their predominant channel type (arterial, venous, capillary, lymphatic, or combined). Venous malformations, often improperly termed "cavernous hemangiomas," are the most common vascular abnormality. By virtue of their embryonic origin, they are present at birth, though often they do not become apparent until somewhat later. Histologically, they consist of mature endothelial-lined channels with insufficient surrounding smooth muscle. This abnormal mural structure allows the lesions to expand slowly over time. Since vascular malformations are not proliferative, they would not be expected to respond to antiangiogenic or any other known pharmacologic agents.

The lesions of BRBNS represent a specialized type of venous malformation. They are typically small, circumscribed, and multifocal. Although they may be present in any body tissue, they predominate in the skin and GI tract. The gastrointestinal lesions may manifest clinically with bleeding or as a lead point for small bowel intussusception. As demonstrated by the patients in our series, the bleeding is typically chronic continual bleeding rather than sudden catastrophic hemorrhage.

The clinical literature regarding BRBNS is limited almost exclusively to case reports. Pharmacologic agents have been used in an attempt to control the chronic blood loss in BRBNS. Antiangiogenic agents such as corticosteroids[7,8] and interferon-α[8] have been used based on the faulty rationale that the lesions would involute similarly to infantile hemangiomas. As for other causes of GI bleeding, octreotide has also been attempted.[9] However, there is no convincing evidence for durable beneficial effects from any drug treatment upon bleeding for BRBNS. Laser photocoagulation[7,14–16] and endoscopic removal[10–13] by a variety of methods have been described, but also in minimal individual reports and without evidence of durable success. Surgical excision has been discouraged because of the frequent multitudes of lesions and the belief that resected lesions would recur.[9,17–21]

Given that there is no currently available pharmacologic agent to effectively treat the GI bleeding and the likelihood that resected venous malformations would not recur, we undertook a strategy of aggressive removal of all the gastrointestinal lesions of BRBNS. If the rationale were sound, all lesions identified, and technical success possible, we believed that the bleeding could be permanently controlled. At our Vascular Anomalies Center, we have evaluated 32 patients with this rare disorder, of whom 10 have been treated surgically. This represents the largest reported clinical experience to date.

We were successful in essentially eliminating bleeding in 9 of 10 patients. One patient, who did not have complete intraluminal evaluation, again experienced clinical bleeding beginning 2 years after his operative procedure. With the exception of this single patient, no other patients have required transfusion after discharge from the hospital. However, 2 other operated patients are known to have GI venous malformations, although without clinically apparent bleeding. One has had only the first of a planned 2-stage operation because of the exceedingly large number of lesions and length of the initial operation. The other patient had evidence of persistent lesions on endoscopic evaluation for symptoms of postprandial abdominal discomfort. This patient had 557 lesions and many were treated by banding or suture ligation during the operation rather than resection. Given this modification of technique and the greater distribution of her currently visualized lesions in the stomach, duodenum, and rectum (areas in which band ligation was performed almost exclusively), it is likely that the intramural portion of some of these lesions may have remained, allowing for apparent

"recurrence." Rather, these are likely residual incompletely removed lesions that have subsequently expanded. This same phenomenon is known to occur after incomplete surgical resection of VM in other body sites as well. For this reason, we suggest caution with the use of ligation techniques, either endoscopic banding or surgical suture ligation, because there may be more risk for incomplete removal of venous malformations, as compared with resective techniques.

From our experience, we believe that serious chronic bleeding from GI venous malformations of BRBNS can be successfully controlled by aggressive resection of the VM, regardless of their number or location. Pharmacologic therapy is unlikely to be of benefit. This aggressive operative approach can help avoid the ravages of chronic anemia, including fatigue, iron overload, and the potential risks of repetitive blood transfusions including hepatitis and allosensitization. Surgical intervention is best planned when a transfusion requirement becomes apparent. Earlier intervention increases the risk of not finding very small lesions that have not had a chance to expand or "ripen." Once an operative approach is chosen, complete visualization of the entire gastrointestinal mucosa from the mouth to the anus must be performed. Complete eradication may avoid the need for repeated operations. Incomplete removal of any given lesion may allow for reexpansion and recurrent bleeding. Although extremely tedious, standard surgical principles and techniques combined with careful anesthetic management allow for a successful outcome with minimal morbidity. Patients with an overwhelming number of lesions may require staged operative procedures. Nevertheless, this approach dramatically improves the health and well-being of patients with BRBNS.

REFERENCES

1. Gascoyen M. Case of naevus involving the parotid gland, and causing death from suffocation. Naevi of the viscera. *Trans Pathol Soc (Lond)*. 1860;11:267.
2. Bean WB. Blue rubber-bleb nevi of the skin and gastrointestinal tract. In: Bean WB. *Vascular Spiders and Related Lesions of the Skin*. Springfield, IL: Charles C Thomas; 1958:17–185.
3. Walshe MM, Evans CD, Warin RP. Blue rubber bleb naevus. *Br Med J*. 1966;2:931–932.
4. Gallione CJ, Pasyk KA, Boon LM, et al. A gene for familial venous malformations maps to chromosome 9p in a second large kindred. *J Med Genet*. 1995;32:197–199.
5. Chen PP, Weishaar PD, Murray TG. Blue rubber bleb nevus syndrome. *J Pediatr Ophthalmol Strabismus*. 1997;34:321–323.
6. McKinlay JR, Kaiser J, Barrett TL, et al. Blue rubber bleb nevus syndrome. *Cutis*. 1998;62:97–98.
7. Dieckmann K, Maurage C, Faure N, et al. Combined laser-steroid therapy in blue rubber bleb nevus syndrome: case report and review of the literature. *Eur J Pediatr Surg*. 1994;4:372–374.
8. Boente MC, Cordisco MR, Frontini MV, et al. Blue rubber bleb nevus (Bean Syndrome): evolution of four cases and clinical response to pharmacologic agents. *Pediatr Dermatol*. 1999;16:222–227.
9. Gonzalez D, Elizondo BJ, Haslag S, et al. Chronic subcutaneous octreotide decreases gastrointestinal blood loss in blue rubber-bleb nevus syndrome. *J Pediatr Gastroenterol Nutr*. 2001;33:183–188.
10. Dwivedi M, Misra SP. Blue rubber bleb nevus syndrome causing upper GI hemorrhage: a novel management approach and review. *Gastrointest Endosc*. 2002;55:943–946.
11. Sala FT, Urquijo PJJ, Lopez VB, et al. Blue nevus syndrome: endoscopic treatment by sclerosis and band ligation. *Gastroenterol Hepatol*. 1999;22:136–138.
12. Bak YT, Oh CH, Kim JH, et al. Blue rubber bleb nevus syndrome: endoscopic removal of the gastrointestinal hemangiomas. *Gastrointest Endosc*. 1997;45:90–92.
13. Shimada S, Namikawa K, Maeda K, et al. Endoscopic polypectomy under laparotomy throughout the alimentary tract for a patient with blue rubber bleb nevus syndrome. *Gastrointest Endosc*. 1997;45:423–427.
14. Morris L, Lynch PM, Gleason WA, et al. Blue rubber bleb nevus syndrome: laser photocoagulation of colonic hemangiomas in a child with microcytic anemia. *Pediatr Dermatol*. 1992;9:91–94.
15. Shahed M, Hagenmuller F, Rosch T, et al. A 19-year-old female with blue rubber bleb nevus syndrome. Endoscopic laser photocoagulation and surgical resection of gastrointestinal angiomata. *Endoscopy*. 1990; 22:54–56.
16. Maunoury V, Turck D, Brunetaud JM, et al. Blue rubber bleb nevus syndrome. 3 cases treated with a Nd:YAG laser and bipolar electrocoagulation. *Gastroenterol Clin Biol*. 1990;14:593–595.
17. Ng WT, Kong CK. Argon plasma coagulation for blue rubber bleb nevus syndrome in a female infant. *Eur J Pediatr Surg*. 2003;13:137–139.
18. Place RJ. Blue rubber bleb nevus syndrome: a case report with long-term follow-up. *Mil Med*. 2001;166:728–730.
19. Wong CH, Tan YM, Chow WC, et al. Blue rubber bleb nevus syndrome: a clinical spectrum with correlation between cutaneous and gastrointestinal manifestations. *J Gastroenterol Hepatol*. 2003;18:1000–1002.
20. Ertem D, Acar Y, Kotiloglu E, et al. Blue rubber bleb nevus syndrome. *Pediatrics*. 2001;107:418–421.
21. Sandhu KS, Cohen H, Radin R, et al. Blue rubber bleb nevus syndrome presenting with recurrences. *Dig Dis Sci*. 1987;32:214–219.
22. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations of infants and children: a classification based on endothelial characteristics. *Plast Reconstr Surg*. 1982;69:412–420.
23. Kassarjian A, Fishman SJ, Fox VL, et al. Imaging characteristics of blue rubber bleb nevus syndrome. *Am J Roentgenol*. 2003;181:1041–1048.
24. Hales K, Connolly LP, Drubach LA, et al. Tc-99m red blood cell imaging of blue rubber bleb nevus syndrome. *Clin Nucl Med*. 2000;106: 835–837.